

VIRUS, PREVIOUS INFECTION

NO. 523-R1

Activated: 10/1/66

THE COUNCIL FOR TOBACCO RESEARCH - U.S.A.

633 THE D AVENUE
NEW YORK, N. Y. 10017

COMMITTEE

Dr. Jacobson, Chm.
Dr. Bing
Dr. Lynch
Dr. Boosli

Application For Research Grant

Date: August 1, 1967

1. Name of Investigator(s): (Include Title and Degrees)

Oswald R. Jones, M.D. - Director of Research Project

2. Institution &

Address: St. Luke's Hospital - West 113th Street, New York City

3. Short Title of Project:

Carbon monoxide uptake and diffusion capacity in children. This test together with others will be used to evaluate pulmonary function in children starting at the earliest age of cooperation. This evaluation of

4. Proposed Starting Date: pulmonary function will be applied to normal children, those with asthma bronchitis, or chronic pneumonia which conditions were subsequent to
5. Anticipated Duration of this Specific Study: particularly those caused by known viral agents. 4. October 1, 1967. - 3-5 years.

6. Brief Description of Objectives or Specific Aims:

Measurements of carbon monoxide (CO) uptake and diffusion capacity (1) have been modified to obviate painful arterial puncture by the use of end tidal PCO at rest (2, 3, 4, 5) and during graded hyperventilation (6). Application of these methods in the dog, and in normal humans and patients with chronic chest diseases have established the relationship between CO uptake and diffusion as graded hyperventilation in normal and diseased adults (7, 10 supporting 8,9)

Normal children will be grouped according to age and size and normal values for CO uptake and diffusion established as controls. Children with asthma bronchitis and post viral pneumonitis will be studied and the results compared.

7. Give a Brief Statement of your Working Hypothesis:

The objectives of the study are: (1) to establish normal values for CO uptake and diffusion capacity at rest and during hyperventilation in children. (2) To study the relationship of asthma, bronchitis and viral pneumonitis on diffusion capacity in children as a background for the development of chronic pulmonary insufficiency

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8. Details of Experimental Design and Procedures: (Attach Separate Pages)

See attached separate page

9. Physical Facilities Available (Where Other than Administering Organization Indicate Geographical location)

The cardiopulmonary laboratory of St. Luke's Hospital is a recognized research laboratory in pulmonary diseases with four full time physicians, three blood gas technicians and all equipment and facilities to perform the studies outlined. New CO measurement and recording equipment is requested for specific application to small children and infants.

10. Additional Requirements

The pediatric department of St. Luke's Hospital is headed by a full time director and operates an active inpatient service of fifty-four beds with 1500 patients per one year, as well as an outpatient department with more than 30,000 visits per one year. A full time pediatric cardiologist will devote part time (1/3) to this project.

10. Additional Requirements

Antibody titre for viruses. Fluorescent antibody search in tissues obtained by biopsy or at post mortem, also cultures of the above tissues for presence of bacteria and viruses.

As mentioned CO uptake and diffusion capacity techniques have been developed in this laboratory which have been validated in adults and which are specifically applicable in children as described.

11. Biographical sketches of all principal and professional personnel (append):

12. List of publications: (Five most recent as pertinent) (append):

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Material and Method

Twenty healthy boys, age 9 to 14 years, from the Cathedral School, and 11 patients from the Pediatric Department of St. Luke's Hospital of a similar age group were studied, for their lung function. Studies consisted of extensive spirometric measurements, lung volume evaluation using helium-dilation method, diffusion studies using carbon monoxide method modified in such a way that correction for CO back pressure was introduced and that multiple results on one person were obtained using graded hyperventilation.

History and clinical examination were performed on all healthy boys. All hospital patients were examined and evaluated by a pediatrician. Hospital patients were categorized as 1) normal, 2) those with minimal lung damage, if any, 3) those with mild lung damage, and 4) those with moderate lung damage. Evaluation of the physiologic studies was done independently, without knowledge of the clinical impressions, and the results were then compared.

Observations

Normal boys: Spirometric and volumetric studies have shown increase in lung volumes related to the growth of the person studied, as expected. The ratios of the subdivisions of the lung volumes did not show any significant difference in this particular span of years.

Diffusion studies have shown an unexpected decline in efficiency of the alveolocapillary membrane when expressed per unit of lung volume for more mature boys. The findings indicate that the size of alveoli changes with age, so that actual alveolocapillary membrane reduces per unit of volume. This can be explained by increase of the size of the alveoli. This is, to our knowledge, the first time that this has been shown physiologically, although this was to be expected because the growth of the lungs by proliferation of the alveolar units stops approximately at the age of ten and after that the lung volume increases essentially by expansion of the alveolar space.

Sick persons: It was found that the majority of the sick individuals have shown a distorted ratio of lung subdivisions (residual volume:total lung volume), although a discrimination toward normal persons was impossible because of the wide span of normal values.

Diffusion studies were able to differentiate sick persons from their healthy age-mates. Even mildly sick persons had their diffusion values at the lower limit of normal or below that limit.

In conclusion, it is possible to show that we have reliable tools for measuring lung functions. The means are so sensitive that they can show the physiological changes related to the body growth in this age group. In addition, the results can discriminately show pathologic reduction in functions caused by chronic lung disease in children.

More studies will be needed to establish definite span of normal values for each age and size group, as well as to evaluate damage induced by different noxious agents.

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Added to our investigative facilities, will be a new diagnostic viral laboratory at St. Luke's where we can identify the causative agent of pulmonary damage in childhood.

13. Budget (1st year)

A. Salaries (Personnel by names)

Professional
Dr. Veljko Krstulovic
Dr. Lucy Swift

% time

Amount

100
33 2/3

Technical

Mr. William Rosenberg

100

Sub-Total

B. Consumable Supplies (list by categories)

Medical gasses
valves
tubing
bags, etc.

~~23,242.00~~

Sub-Total

2,000.00

C. Other Expenses (itemize)

23,242.00

23,242.00

Sub-Total

D. Permanent Equipment (itemize)

CO analyzer
Recorder

2,800.00

2,900.00

28,942.00

E. Overhead (15% of A+B+C)

3486.30

Total

32,428.30

Estimated Future Requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Overhead	Total
Year 2	Same	Same		None	Same	26,728.30
Year 3	Same	Same		None	Same	26,728.30

It is understood that the applicant and institutional officers in applying for a grant have read and found acceptable the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Signature

Director of Project

Signature

Business Officer of the Institution

Telephone

Telephone

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4.

Other Sources of Financial Support

List financial support for research from all sources, including own institution, for this and/or related research projects.

Current

Title of Project
Emphysema and Measles

Source

Stony Wold Corporation

Amount

\$9,000

Duration

1
year

Pending

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CURRICULUM VITAE

OSWALD R. JONES, M.D.

R R Waterbury, Conn. B.S., 1919 Yale College,
 M.D. Columbia 1923. St. Luke's Hospital., N.Y. med. 1923-25, Bellevue
 Hosp., N.Y. chest serv. 1925-26, ass't path. St. Luke's Hosp., 1926-27.
 Inst. in Med. Col. Univ. 1927-32. Assoc. in Med. 1932-37. Asst. Clin.
 Prof. of Med. 1937-62. F.A.C.P. Dipl. Int. Med., Ac. Med., Dir.
 Cardio Respiratory Lab. St. Luke's. Cons. phy. St. Luke's., Cons. Phy.
 chest dis. Southampton Hosp., Cons. phy. chest service Bellevue Hosp.

References:

1. Jones, O.R.: Measles - A Cause of Emphysema, An Hypothesis Concerning Chronic Pulmonary Emphysema, a Possible Cause and its Prevention, Am. Rev. Resp. Dis. Vol. 87, 4, Apr. 1963
2. Jones, O.R., Platt, W.D., and Amill, L.A. - Miliary Tuberculosis Caused by Intravenous Self-Injection of Tubercle Bacilli, Treated Successfully with Streptomycin Therapy., Am. Rev. of T.B., Vol. 60, No. 4 Oct. 1949
3. Jones, O.R. and Courmand A. - The Shrunken Pulmonary Lobe with Chronic Bronchiectasis., Am. Rev. of T.B. Vol. 28, No. 3 Sept. 1933
4. Miller, J.A., and Jones, O.R. - Primary Carcinoma of the Lung. Am. Rev. of T.B. Vol. 21, No. 1, Jan. 1930
5. Jones, O.R. and Burford, G.E. - Massive Atelectasis following Cyclopropane Anesthesia - Jour. A.M.A. Vol. 110, Apr. 2, 1938.

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CURRICULUM VITAE

LUCY H. SWIFT M.D.

R R New York City, Barnard College, New York City
 1949, A.B., College of Physicians & Surgeons, Columbia University, N.Y.C.
 M.D. 1953. Mary Imogene Bassett Hospital, Cooperstown, N.Y. 1953 (July-Dec.)
 St. Luke's Hosp. N.Y.C., 1960-62, clin. fellow pediatric cardiology 1962-
 1964, Presbyterian Hosp. Barnes Hosp. N.Y.C., Res. Assoc. pharm. 1954-1955
 Div. Exp. Chemotherapy, Sloan-Kettering Inst. N.Y., Med. Lic. N.Y.S. 1962,
 Am. Bd. of Ped. Dipl. 1965, Instr. Pediatrics Columbia Univ. 1964-,
 Asst. Att. Ped.(Cardio) St. Luke's Hosp. 1964-, Ass. Ped. Columbia-Pres.
 Med. Center, N.Y.C. 1964 - Assoc. Visiting Ped., Harlem Hosp. N.Y. 1965-,
 Med. Soc. of County of N.Y., N.Y.State Med. Soc. Amer. Med. Assoc.

References

1. Swift, L.H., and Griffiths, S.P.: Cardiac Arrhythmias in the First Year of Life; The Heart Bulletin 14: 113-116, 1965 (Nov. Dec.)

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Chronological Listing of All Activities Since Graduation
From Professional School

FROM

TO

Month	Year	Month	Year	Type of Activity, including Name and Address of Employer, Beginning with Date of Graduation from Professional School
	1936			Baccalaureate from Second State's Boys Gymnasium, Zagreb.
Oct.	1941			Graduation from Medical School of the University of Zagreb.
Nov.	1941	May	1942	Internship in Pediatrics, Dermatology & Gynecology at The University of Zagreb.
May	1942	Feb.	1943	Continuation of Internship in the Chief Army Hospital, Zagreb.
				<u>Postdoctoral Training:</u>
Aug.	1947	Oct.	1947	Course in Aviation Medicine, Zemun, Yugoslavia
July	1950	Nov.	1951	While in the army, attended daily medical conferences, ward rounds, cardiac conferences and EKG reading in Medical Department of University Hospital in Zagreb. Chief, Dr. Ivan Botteri, Professor of Clinical Medicine.
Dec.	1951	Dec.	1954	Residency in Internal Medicine at University Hospital. Chief, Dr. Ivan Botteri, Professor of Clinical Medicine, succeeded by Dr. Arpad Hahn, Professor of Clinical Medicine.
Jan.	1955	Dec.	1956	Residency in Cardiology at University Hospital. Dr. Radovan Ivancic, Associate Professor in Medicine.
July	1957			Board of Internal Medicine. Croatia-Yugoslavia.
				<u>Professional Appointments</u>
Feb.	1943			Medical Officer in Yugoslav Army.
April	1945	July	1947	Medical Officer in Air Force battalion (equivalent to flight surgeon in U. S. Air Force). 1003546713
July	1947	Nov.	1951	Chief of Clinical Medicine in Air Force Division.
Dec.	1951	Jan.	1957	Instructor in Medicine at Medical School, University of Zagreb. Chief, Dr. Ivan Botteri and Dr. Arpad Hahn, Professor in Clinical Medicine.

Veljko Joseph Krstulovic, M. D.

FROM		TO		Type of Activity, including Name and Address of Employer, Beginning with Date of Graduation from Professional School
Month	Year	Month	Year	
Feb.	1957	June	1960	Chief of Cardiopulmonary Section of Internal Medicine Polyclinic at Medical School in Zagreb. Chief, Dr. Vinko Vuletic, Professor of Clinical Medicine.
July	1957	June	1960	Associate Supervisor in Charge of Physical Diagnosis Course at the Medical School in Zagreb. Chief, Dr. Vinko Vuletic, Professor of Clinical Medicine.
July	1960	June	1961	Research Fellow at Cardiovascular Lab at Cornell Medical School. Chief, Dr. Irving S. Wright, Professor of Clinical Medicine, Cornell Medical School.
July	1961	Dec.	1964	Research Fellow in Cardiopulmonary Laboratory at St. Luke's Hospital Center, New York City. Chief, Dr. A. L. Loomis Bell, Jr.
Jan.	1965	present		Research Associate in Cardiopulmonary Laboratory at St. Luke's Hospital Center.
May	1966	present		Consultant for Heart and Lung Diseases, Harlem Hospital.

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Veljko Joseph Krstulovic, M.D.

List of Publications in Yugoslavia

- 1) Krstulovic, V.: Dyspnea as a medical emergency. *Radovi Medicinskog Fakulteta u Zagrebu*. 1: 72, 1955.
- 2) Krstulovic, V., Ivancic, R.: Hemodynamics of mitral valvular disease. *Liječnički Vjesnik*. 79: 365, 1957.
- 3) Krstulovic, V.: Cardiopulmonary functions in normals and in subjects with chronic pulmonary diseases. *Tuberculosis*. 10: 132, 1958.
- 4) Oberhofer, T., Pitamic, T., Gvozdenovic, V., Krstulovic, V.: Dextrocardia combined with cardiovascular malformations. *Pediatrics iugoslavica*. 2: 297, 1960.
- 5) Galinovic, N., Bunarevic, N., Krstulovic, V.: *Candida albicans* mycelium in the left atrium imitating clinical finding of intermittent mitral stenosis in a case of pulmonary moniliasis. *Medicinski glas*. 1961.
- 6) Ivancic, R., Krstulovic, V.: *Electrocardiography*. Skolska knjiga, Zagreb. 1960.
- 7) Krstulovic, V.: Venous pressure and circulation time as a differential diagnostic mean in cardiopulmonary disturbances. In press.
- 8) Krstulovic, V., Gvozdenovic, V., Hauptman, E.: Splenic pulp pressure correlated with spleno portal angiography in patients with portal hypertension and in patients with splenic artery thrombosis. In press.

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List of Publications in United States of America

- 1) Shimomura, Seiichi, Pierson, Richard N., Jr., Krstulovic, Veljko, and Bell, A. L. L., Jr.: Primary and secondary pulmonary vasopressor responses to acetylcholine demonstrated by the wedged catheter perfusion technique. (Abstract), Bull. N. Y. Acad. Med., 38: 839, 1962.
- 2) Bell, A. L. L., Jr., Kightlinger, Benjamin, Shimomura, Seiichi, and Krstulovic, Veljko: Postvalvular pulmonary artery stenosis. Hemodynamic and radiologic definition. Circ. 26: 685, 1962. (Abstract).
- 3) Shimomura, Seiichi, Krstulovic, Veljko, Pierson, Richard N., Jr., and Bell, A. L. L., Jr.: Separation of the primary vasoconstrictor effect of acetylcholine in the pulmonary vascular bed from systemically induced response utilizing the wedged perfused segment in the intact dog. Circ. 26: 785, 1962. (Abstract).
- 4) Kightlinger, Benjamin N., Shimomura, Seiichi, Krstulovic, Veljko, Kittredge, Richard D., and Bell, A. L. Loomis, Jr.: Postvalvular pulmonary artery stenosis. Hemodynamic and radiologic definition (Abstract), Bull. N. Y. Acad. Med. 39: 58, 1963.
- 5) Haynes, W. F., Jr., Krstulovic, V. J., Bell, A. L. L. Jr.: Smoking habit and incidence of respiratory tract infection in group of adolescent males. Am. Rev. Resp. Dis. 93: 730, 1966.
- 6) Krstulovic, V. J., Haynes, W. F., Jr., and Bell, A. L. L. Jr.: Spirometry in adolescent males. I.. Normal values. Submitted for publication.
- 7) Krstulovic, V. J., Haynes, W. F., Jr., and Bell, A. L. L. Jr.: Spirometry in adolescent males. II. Comparison of spirometric data. Submitted for publication.
- 8) Krstulovic, Veljko: Graded hyperventilation for evaluation of dynamics of diffusion. In preparation.
- 9) Krstulovic, Veljko J., Felton, Charles, and Bell, A. L. L. Jr.: Effect of respiratory rate on lung diffusion using graded hyperventilation. In preparation.
- 10) Krstulovic, Veljko J., Jones, Oswald R., Bell, A. L. L. Jr.: Age related changes in the efficiency of the alveolar capillary membrane in children obtained by hyperventilation diffusion study. In preparation.

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